Variant Classification Criteria

Variants were classified and reported based on ACMG, ACGS-2020v4.01 and ClinGen SVI WG guidelines (Richards et al., 2015, PMID: 25741868; Ellard et al., 2020, Association for Clinical Genomic Science; https://clinicalgenome.org/working-groups/sequence-variant-interpretation/). For variants most recently assessed after 2022-03-03, we provide the applied ACMG criteria and their respective strength in the comment section.

Only variants (SNVs/Small Indels) in the coding region and the flanking intronic regions (±8 bp) with a minor allele frequency (MAF) < 1% are evaluated. Known disease-causing variants (according to HGMD® and ClinVar database) are additionally evaluated if located outside of coding regions and up to 5% MAF. Minor allele frequencies are taken from public databases (e.g., gnomAD) and an in-house database. X-chromosomal variants that are listed in public databases equal to or greater than 50 times in a hemizygous state and are not disease-causing variants according to HGMD are excluded from analysis. Synonymous variants in mitochondrially encoded genes are classified as benign. In silico predictions were performed using the programs MetaLR (Dong et al., 2015, PMID: 25552646), PrimateAI (Sundaram et al., 2018, PMID: 30038395), APOGEE (Castellana et al., 2017, PMID: 28640805) and SpliceAI (Jaganathan et al., 2019, PMID: 30661751). This prediction can be complemented with additional in silico predictions in individual cases.

The evaluation of variants is dependent on available clinical information at the time of analysis. Variants are named according to the HGVS recommendations without any information regarding the cis or trans configuration. Large scale copy number variants are named according to current ISCN guidelines. Described diseases and gene information catalogues in use include OMIM (www.omim.org), Orphanet (www.orpha.net), GeneReviews (http://www.ncbi.nlm.nih.gov/books/NBK1116/), DECIPHER (https://decipher.sager.ac.uk), Database of Genomic Variants (DGV; http://dgv.tcag.ca/dgv/app/home), HPO (https://hpo.jax.org/app/), MITOMAP (https://www.mitomap.org/MITOMAP) to give indications of mechanisms of disease, inheritance patterns, phenotypic spectra, abundance as well as expressivity and penetrance.

Last updated: 24.10.2023